ALBERTA HERITAGE FOUNDATION
FOR MEDICAL RESEARCH

TechNote

TN 47 JULY 2004

GABAPENTIN FOR NON-MALIGNANT CHRONIC PAIN

Request: This response addressed a request from the Information Sharing Group on Chronic Pain (ISGCP). The ISGCP has been examining the effectiveness of different interventions for chronic pain in rural settings where access to central programs may be unavailable. The objective of this TechNote is to describe the background and the current evidence on the safety and efficacy/ effectiveness of gabapentin when used in the management of non-malignant chronic pain.

BACKGROUND

Chronic pain is a complex condition, more prevalent in elderly people [1], which creates distress and disability and is recognized as a major public health problem [2-8]. It affects 10% to 20% of the American population [9] and over 18% of the Canadian population suffer from severe chronic pain [10]. The estimated annual cost of chronic pain exceeds $10 billion in Canada [10].

In Alberta, chronic pain is most likely to be reported in chronic conditions such as arthritis, back pain, migraine headache, epilepsy, stroke, and diabetes [11]. These chronic pain states (associated with progressive but non-malignant disease) are referred to as non-malignant chronic pain.

Non-malignant chronic pain

Non-malignant chronic pain (NMCP) is defined here as "pain not associated with cancer that exists beyond an expected time frame for healing (usually taken to be three or six months) and associated with protracted illness or as a symptom of a recurring

Technotes are brief reports, prepared on an urgent basis, which draw on limited reviews and analysis of relevant literature and on expert opinion and regulatory status where appropriate. They are not subject to an external review process.

condition". This definition was used in previous reports in the series on the management of chronic pain [3, 9, 12].

Currently, there is no consensus on the terminology or classification systems used to define NMCP states [2]. For treatment purposes NMCP states have been grouped into nociceptive pain (due to injury or disease outside the nervous system), neurogenic/ neuropathic pain (caused by damage to nerves or nerve paths), primarily psychogenic pain (psychologically mediated), and mixed or unspecified pain (caused by a mixed or unknown mechanism) [4-7, 13]. Each class of NMCP states varies in characteristics, etiliology, onset of symptoms and response to treatment.

Management of NMCP

Since NMCP has multiple etiologies and pathophysiologic manifestations, treatment requires a multidisciplinary approach by a combination of pharmacological and non-pharmacological treatments [2-8, 11, 13, 14]. Pharmacotherapy remains the core of treatment and prescribed agents include opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants and anticonvulsants, used alone or in combination.

No single class of agents has been found to be effective for all types of NMCP, presumably because pain syndromes involve different mechanisms [14-21]. The pharmacokinetic profiles of these agents and the potential for frequent adverse effects, some of which may be disabling and life threatening, may limit their use particularly for elderly patients. A main disadvantage in this population is the potential for drug-drug interactions.

As the underlying mechanisms of various types of NMCP continue to be elucidated, attention has been focused on the use of newer generation of anticonvulsants as adjunct analgesics. Adjunct analgesics are medications with a primary indication other than pain management that may provide relief and control in some painful conditions. Gabapentin is one of these agents.

GABAPENTIN

Gabapentin (GBP) is an aminoacid structurally related to gamma-aminobutyric acid (GABA), a widely distributed inhibitory neurotransmitter involved in the transmission and modulation of pain signals in the nervous system [21-24]. It is used as an add-on therapy in patients with partial seizures resistant to conventional therapies. Many investigators believe GBP has multiple mechanisms of action, which would justify its use in many clinical conditions besides epilepsy, including management of NMCP [14, 16, 18, 20, 22, 23, 25-32]. However, the mechanism(s) by which it exerts its analgesic action has yet to be fully elucidated.

Description

GBP is available only as oral preparations (supplied in capsules, tablets, and oral solution) [14, 20, 32-36]. Brand names include Neurontin®, Apo®-gabapentin, Novo®-gabapentin, and PMS®-gabapentin [33-37]. Neurontin® (Pfizer Pharmaceuticals) is the formulation used in clinical studies including patients suffering from NMCP.

GBP (Neurontin®) is rapidly absorbed, with inter-individual and dose-dependent variability in bioavailability [14, 16-18, 20, 21, 23, 24, 26, 29-32, 34-36, 42-44]. It is eliminated entirely via the kidney and it is not metabolized in humans. It does not bind to plasma protein and does not interfere with hepatic function. It has no known significant pharmacokinetic interactions with other adjunct analgesics (such as antidepressants and older generation anticonvulsants). GBP showed interaction with antiacids and morphine [20, 25, 32-36].

Side effects, contra-indications and cautions

GBP is usually well tolerated, and it is not associated with anticholinergic side effects, hematological reactions or hepatic problems [14, 18, 20, 22, 26-28, 31, 32, 34-36, 40, 43-48]. However, it is associated with symptoms and signs of central nervous system depression and may impair patient's cognition and ability to operate. The most commonly reported side effects are somnolence, dizziness, sedation, fatigue and ataxia. Other reported side effects include peripheral edema, blurriness of vision, ataxia, gait and balance problems, depression, weakness, headache, frequent urination, tremor, indigestion, diarrhea, and nausea. These side effects, usually transient and minor, require monitoring and dosage adjustment.

The presence of other medical problems may affect the use of GBP, particularly kidney disease [20, 32-36]. Dosage adjustment in patients with compromised renal function or undergoing hemodialysis is recommended.

GBP is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients [14, 33-36]. It has been recommended to use it cautiously in pregnancy and it is not recommended for mothers who are breast feeding.

Indications and usage

GBP (Neurontin®) is indicated as an adjunctive therapy to treat partial epilepsy and as an adjunctive analgesic in the management of post-herpetic neuralgia (PHN), a form of chronic neuropathic pain [22, 31, 34-36, 39, 40, 49]. For PHN patients, it is recommended to start GBP treatment at 100-300 mg/day with titration if necessary to a maximum of 3,600 mg/day (administered in three divided doses) [14, 31, 34, 36, 38-41]. The target dose (which demonstrated therapeutic effect) is 1800 mg/day.

Various off-label uses (unapproved indications) have been reported for GBP including painful diabetic neuropathy (PDN), trigeminal neuralgia (TN), NMCP associated with various disorders (including multiple sclerosis, spinal cord injury, and stroke), migraine

headaches, deficit disorder, restless legs syndrome, periodic movement disorder of sleep, somatization disorder, bipolar disorder, and drug and alcohol withdrawal syndromes [14, 17, 19, 21, 22, 26-29, 31, 40, 43-48, 50, 51].

Regulatory status in North America

In Canada, GBP (Neurontin®) is available as an anticonvulsant [33, 37] and has a Notice of Compliance only for the management of patients with epilepsy who failed to control their seizures with conventional therapy (Health Canada, personal communication).

In addition to its use as an adjunct therapy for partial epilepsy, GBP (Neurontin®) was approved in the United States of America (USA) by the Food and Drug Administration (FDA) for the management of PHN [35, 36, 52].

AVAILABLE EVIDENCE

This TechNote response is based on a review of systematic reviews conducted on the use of GBP in the management of NMCP. Selected for data extraction were only published reports of systematic reviews that, by virtue of design and quality of reporting [53-55], were most likely to provide high level of evidence. Individual randomized controlled trials (RCTs) published subsequent to the selected systematic reviews are not included.

Only three of the reviews yielded by the literature search [56-58] met the inclusion criteria as described in the methodology section (see Appendix A, Table 1). All have examined the use of GBP for neuropathic pain (particularly PHN and PDN). The other published reviews have examined other indications in the management of NMCP, such as migraine prophylaxis. However, they did not meet all criteria for a systematic review and were excluded from this report (see Appendix A, Table 1). No primary or secondary research on the use of GBP for other forms of NMCP is presented.

The following commentary summarizes the findings reported by the selected systematic reviews. Details of these studies are provided in Tables 2 and 3 (see Appendix B). Information on ongoing research on the use of GBP in the management of NMCP is also provided.

Systematic reviews

Wiffen et al. [56] published a Cochrane Review that evaluated the effectiveness and safety of anticonvulsant drugs in the management of acute and chronic pain. Numbers-needed-to-treat (NNT) were calculated for effectiveness and numbers-needed-to- harm (NNH) for minor and major adverse effects, for individual studies and for pooled data.

The study reviewed 23 RCTs reporting on the use of various anticonvulsants (carbamazepine, phenytoin, GBP, sodium valproate and clonazepam). Only two of the reviewed RCTs evaluated the use of GBP (versus placebo), one for management of

chronic pain associated with diabetic neuropathy (PDN) and one for management of PHN. In both studies, the doses used for GBP (up to 3,600 mg/day) were higher than 1800 mg/day, the dose licensed by FDA for PHN [31]. In both RCTs, treatment duration was 8 weeks (4 weeks titration to maximum tolerated dose, then 4 weeks stable dose).

The analyses of the results reported by the reviewed RCTs, showed that GBP (up to 3,600 mg/day, for 8 weeks) is effective in PHN and PDN in terms of pain relief but does not appear to be superior to carbamazepine (200mg to 600mg daily, for 2 weeks) or phenytoin (300 mg per day, for 2 weeks) [56]. For PDN (one RCT for each drug), the calculated NNT values were 3.8 (95% CI: 2.4-8.7) for GBP; 2.3 (95% CI: 1.6-3.8) for carbamazepine; and 2.1 (95% CI: 1.5-3.6) for phenytoin. The NNH values for "minor harm" were 2.5 (95% CI: 2.0-3.2) for GBP; 3.7 (95% CI: 2.4-7.8) for carbamazepine; and 3.2 (95% CI: 2.1-6.3). The NNHs for "major harm" were not statistically significant for any drug compared to placebo.

For any neuropathic pain carbamazepine had a NNT value of 2.5 (95% CI: 2.0-3.4) and GBP had a NNT value of 3.7 (95% CI: 2.6-4.9) [56]. The NNH values were 3.7 (95% CI: 2.4-7.8) for carbamazepine and 2.5 (95% CI: 20-3.2) for GBP. In other words, *"66% of patients (95 % CI: 61%-71%) who receive either gabapentin or carbamazepine for neuropathic pain will obtain good relief"*.

The reviewers noted that high quality studies of the relative effectiveness of different anticonvulsants in chronic pain syndromes, and for comparisons of antidepressants with anticonvulsants were still needed.

Collins et al. [57] conducted a comparison of published evidence on the efficacy and toxicity for anticonvulsants (GBP, phenytoin, and carbamazepine) and antidepressants (tricyclic antidepressants and selective serotonin reuptake inhibitors) as analgesics in PDN and PHN. The two pain conditions were chosen according to strict diagnostic criteria (previous herpes zoster infection and diabetes). The relative efficacy was evaluated by comparing each drug with placebo. Calculation of the NNT for benefit and NNH for minor and major adverse effects allowed for the quantitative comparison between drugs and drug classes.

Selected were 19 placebo-controlled RCTs evaluating antidepressants and five placebo-controlled RCTs evaluating anticonvulsants [57]. Five studies lasted for ≤ 3 weeks and three studies lasted for ≥ 4 weeks (maximum 6 weeks). The information on study duration for the remaining studies is not provided in the published report of this systematic review. The reviewed five placebo-controlled RCTs evaluating anticonvulsants in PDN and PHN were the same RCTs included in the Cochrane Review [56].

As the majority of reviewed RCTs used a cross-over design the results were presented in terms of "patient episodes" rather than actual numbers of patients[57]. One patient

episode represents the result for one patient completing one part of the cross-over. The studies either titrated the dose of the active treatment to the maximum tolerable level for the individual patient, titrated the dose against plasma concentration, or used a fixed dose within usual recommended ranges.

When RCT data for both pain conditions were pooled, both antidepressants and anticonvulsants had an analgesic effect when compared to placebo[57]. Since the 95% confidence intervals overlapped for both pain conditions, no conclusion could be drawn as to which drug class was more effective. Also, there was no evidence that either drug class was more effective in one pain condition or another. When data were pooled across both pain conditions, the calculated values for NNT were the same for both drug classes, 2.9 (95% CI: 2.4-3.7). This indicates that for every three patients receiving an antidepressant or an anticonvulsant one experienced over 50% pain relief that would not have with a placebo.

The NNH for minor adverse effects was 2.7 for both antidepressants and anticonvulsants (data were pooled across both pain conditions). However, the relative risk estimate showed that the incidence of major adverse effects (those leading to withdrawal from the trial) was significantly greater for antidepressants compared to placebo. The NNH for major adverse effects was 17 (95% CI: 11-43) for tricyclic antidepressants. No statistically significant difference was found in the incidence of major adverse effects between anticonvulsants and placebo.

Collins et al. [57] compared the difference in the incidence of major adverse effects between the drugs and drug classes also by using the ratio between treatment specific benefit and treatment specific harm. For all antidepressants the ratio was 6 indicating that for every six patients experiencing at least 50% pain relief with antidepressants, one will experience an adverse effect severe enough to discontinue treatment. The ratio was 5 for tricyclic antidepressants. The ratio was 8 for all anticonvulsants, 6 for GBP and 9 for phenytoin/carbamazepine. These results suggest that, although there were fewer study withdrawals following treatment with anticonvulsants compared with antidepressants, the magnitude of the difference was relatively small.

When GBP (titrated to between 300 and 3,600 mg per day) was compared to the other anticonvulsants, there were no statistically significant differences in benefit and incidence of adverse effects [57]. The efficacy data for phenytoin (dose fixed at 300 mg/day) and carbamazepine (titrated to between 200 and 600 mg/day) were pooled for both pain conditions (166 patient episodes) and compared with that for GBP (380 patient episodes) [57]. All anticonvulsants were superior to placebo. The NNH for minor adverse effects (data from two RCTs on GBP and two RCTs on phenytoin) were 2.6 for GBP and 3.2 for phenytoin.

These findings show that *"both drug classes are effective, with (combining the two syndromes) at least 50% pain relief achieved in two-thirds of patient episodes treated with*

anticonvulsants and in half treated with antidepressants. This efficacy comes with a similar adverse effect burden." [57] The reported results suggest that GBP is as efficacious in treating PHN and PDN with no significant difference in minor adverse effects and with low incidence of major adverse effects compared to other anticonvulsants and antidepressants.

The sensitivity analyses conducted by Collins et al. [57] highlighted some methodological considerations for future research. The findings indicated that neuropathy scales examining multiple different symptoms, including pain, may underestimate pain relief achieved if the scale is presented as an overall result. The difference observed in the placebo event rate between the trials in PDN and the trials in PHN has implications for the traditional belief that placebo effects are constant within and across condition. In PDN trials, at least 50% pain relief was achieved in 32% of patient episodes compared with 11% of patient episodes in PHN trials.

Mellegers et al. [58] conducted a systematic review of the published evidence on the efficacy/effectiveness and side effects of GBP for the management of neuropathic pain as reported by controlled and uncontrolled clinical trials. Efficacy was assessed through a meta-analysis of RCTs, and the effectiveness in uncontrolled studies was assessed via a system of dichotomous classification of *"bad"* versus *"good"* results. Thirty uncontrolled studies and six RCTs met the inclusion criteria. These studies included a total of 727 patients with multiple neuropathic pain conditions.

A meta-analysis of two placebo-controlled RCTs on GBP (one in PDN and one in PHN), rated as high-quality RCTs, showed positive effect of GBP in terms of pain relief [58]. Wiffen et al. [56] and Collins et al. [57] reviewed the same two RCTs. Subjects' and clinicians' global impression of change or improvement in pain resulted in a relative benefit of 2.44 (95% CI: 1.8, 3.31) and 2.65 (95% CI: 1.86, 3.78). These data suggest that patients receiving GBP had 2.4 more chances of reporting a global impression of improvement in pain than those receiving placebo and clinicians had 2.6 more chances of reporting a global impression of improvement in GBP-treated patients than in those receiving placebo. Quality of life, "profile of mood status", "sleep scores", and "vigor/activity" were also measured in these two RCTs but meta-analyses of these data were not performed.

The addition of data from another two placebo-controlled RCTs, rated as low-quality, did not alter the magnitude or direction of observed positive effect [58]. These studies evaluated the use of GBP (up to 900 mg/day) in patients with PDN (a total of 70 participants) for 6 weeks (in one RCT) and for 3 months (in the other RCT).

The authors noted that the comparison of GBP with other treatment options for neuropathic pain still needs to be investigated in large, well designed RCTs [58]. The reviewed data, obtained from two small sample RCTs (a total of 50 participants), did not allow firm conclusions. The two RCTs compared the analgesic efficacy and safety

of GBP with those of amitriptyline in patients with PDN. They reached a broadly similar conclusion that both drugs achieved similar efficacy. One RCT (open label pilot study, criticized for lack of blinding) indicated that the side effect profile of GBP (up 2,400 mg/day for 12 weeks) was superior to that of amitriptyline (maximum 90 mg/day for 12 weeks)). The other RCT (double blind cross-over trial, criticized for using sub-therapeutic dosing of GBP) showed no difference in the incidence of side effects between the two drugs. In this RCT patients were randomly assigned to receive GBP (900 to 1800mg/day) or amitriptyline (25 to 75 mg/day) for 6 weeks.

The reviewed uncontrolled studies demonstrated a positive effect on pain in different neuropathic syndromes, as well as a benefit on different types of neuropathic pain (allodynia or touch-evoked pain, and burning and lancinating/paroxysmal pain) [58]. However, better response of one pain versus another could not be ascertained. The highest dose administered and the rate-of-dose escalation showed wide variability between studies. In most studies the maximum daily dose varied between 100 mg (single dose) and 1,200 mg (divided doses). In some studies the dose was fixed throughout the study period, whereas in others the maximum dose was achieved within 1 to 2 weeks. Fewer and less severe side effects were reported in the uncontrolled studies.

Based on their findings, the reviewers concluded that GBP *"seems to be effective in multiple painful neuropathic conditions"* and for several pain types (spontaneous ongoing or paroxysmal and stimulus evoked pain). The effectiveness of GBP might be reduced if administered in very low doses, whereas rapid titration might be associated with increased central nervous system side effects. Well-designed RCTs *"may provide true insight into differential responses of pain types to the drug"*.

Upcoming research

An ongoing Cochrane Review by **Chronicle and Mulleners** [59] aims to describe and assess the evidence from controlled trials on the efficacy and tolerability of anticonvulsants for preventing migraine attacks in adult patients (≥ 18 years of age). Considered for inclusion are only randomized and pseudo-randomized clinical trials, comparing anticonvulsants to placebo, no intervention, other drug treatments, and behavioural or physical therapies. The analysis will include only drugs and dosages that are commercially available. The list of target drugs includes GBP. The review is expected to be published in the Cochrane Library Issue 3, 2004.

Another Cochrane Review is currently ongoing to assess the absolute and comparative efficacy and tolerability of both pharmacological and non-pharmacological therapies for the treatment of central neuropathic pain syndromes in patients with multiple sclerosis (MS) [60]. Considered for inclusion are only double-blind RCTs, either placebo-controlled or comparing two or more agents. The list of target drug classes includes

anticonvulsants, shown to be useful as analgesics in neuropathic pain conditions. The review was expected to be published in the Cochrane Library Issue 1, 2004.

The Swedish Council on Technology Assessment in Health Care is currently conducting a study to assess the scientific evidence concerning treatment and care of patients with non-malignant chronic pain (http://www.sbu.se). This assessment will cover the treatment of chronic pain in all age groups and in both men and women. Ethical, social, and economic factors will also be addressed.

Primarily, the assessment will include RCTs reporting on clinically relevant endpoints, but observation studies and qualitative studies may also be considered for outcome measures such as quality of life. Systematic reviews of good quality may be included. The study is expected to be completed and published in 2005.

Patients are being recruited for a double blind RCT on the use of GBP for reducing symptoms of fibromyalgia (http://www.clinicaltrials.gov). The study will include approximately 150 participants who will be randomly assigned to take either GBP or placebo for a 12-week period. The effectiveness will be evaluated using questionnaires to assess fatigue, stiffness, sleep, mood, tender point pain threshold, and quality of life.

GUIDELINES

This section summarizes the recommendations issued on the use of GBP for NMCP provided by the most recently published clinical practice guidelines revealed by the literature search.

The Washington State Department of Labor and Industries and Washington State Medical Association developed a guideline on the use of GBP (Neurontin®) for the management of neuropathic pain, released in 2002 [61]. The guideline is based on a literature review of the scientific information and on expert opinion from actively practicing physicians. According to this guideline:

- Neurontin® is most likely to be effective when it is prescribed for neuropathic pain conditions such as : peripheral nerve injury; peripheral polyneuropathy; Cauda equina syndrome; spinal cord injury ; Complex Regional Pain Syndrome Type II; HIV and cancer related neuropathies; chronic radiculopathy; and other conditions with objective findings of nerve injury and a clearly documented history of neuropathic symptoms.
- Neurontin® is less likely to be effective when it is prescribed for questionable neuropathic pain conditions with no objective finding of nerve injury, such as Complex Regional Pain Syndrome Type I.
- There is no credible scientific evidence that Neurontin® is effective in relieving pain associated with the following non-neuropathic pain conditions: acute musculoskeletal pain; primary somatic pain from chronic musculoskeletal

strain/sprain; low back pain without radiculopathy; tendinitis; and repetitive strain without evidence of entrapment neuropathy.

The type of supporting evidence for each recommendation was not specifically stated.

An Expert Panel at the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain developed a guideline on the advances in neuropathic pain and issued recently recommendations on diagnosis, mechanism and treatment for this condition [31]. The guideline recommends GBP as one the the treatment options that can be used as an initial treatment for *"neuropathic pain in certain clinical circumstances"*. These recommendations for using GBP as a first-line pharmacologic treatment are based on positive results from multiple randomized controlled trials.

Discussion

GBP (Neurontin®) has been studied and reported to be useful for the management of various NMCP states. Most of the published studies have been uncontrolled and open-label, but RCT data have also been reported [22, 31]. The RCTs examined the use of GBP in PHN, PDN, mixed neuropathic pain syndrome, phantom limbs, Guillain-Barre syndrome, migraine prophylaxis, and NMCP secondary to spinal cord injury. The most extensive studies have been with PHN and PDN.

According to the selected systematic reviews, GBP has been proven to be more effective than placebo for the treatment of PDN and PHN [56-58]. GBP showed significant pain relief with minimal adverse effects and improvement across measures of sleep, mood state, quality of life, and subject- and clinician-based assessments of change. It has been relatively well tolerated, with somnolence, dizziness, sedation, fatigue and ataxia being the most commonly observed side effects. However, based on the reviewed RCT data the most efficacious dose was not entirely clear. GBP was titrated to between 300mg and 3600 mg per day [57, 58]. The treatment duration has been short (≤ 3months) [57, 58] and its long-term efficacy, safety and tolerability are still unknown.

Given the reported efficacy of GBP in PHN and PDN, a clinically relevant question is whether GBP is equivalent or superior to alternative options. Only a few trials have directly compared GBP with other adjuvant analgesics commonly used for these forms of NMCP [21, 22, 31, 40, 43-46, 48, 50, 56-58, 62]. It is not clear yet whether its therapeutic effects, tolerability and safety are better than those of older generation anticonvulsants or antidepressants.

The selected systematic reviews did not locate any published studies reporting on direct comparisons between GBP and other anticonvulsants [56-58]. Two systematic reviews [56, 57] indirectly compared GBP to carbamazepine and phenytoin, and found GBP not to be superior to these anticonvulsants in terms of good pain relief and incidence of adverse effects.

The reviewed evidence obtained from two small RCTs of short duration comparing GBP with amitriptyline in PDN patients is not conclusive. Both drugs were found to be equivalent in terms of pain relief when measured by pain scales and global pain scores [58]. However, no clear evidence was provided to show a better tolerability and side effect profile for GBP in this population.

Collins et al. [57] showed that both antidepressants and anticonvulsants were superior to placebo in PHN and PDN. Although the type of adverse effects associated with the two drug classes differed, the incidence of minor adverse effects was the same. There were fewer major adverse effects following anticonvulsants, but the magnitude of the difference was relatively small.

The pharmacokinetic and side effect profiles of the antidepressants and older generation anticonvulsants limit their use in some patients with PHN and PDN thus warranting consideration for GBP [8, 21, 22, 25, 28, 31, 38, 44, 45, 48, 50, 63, 64], particularly in the case of the elderly, who are sensitive to these medications and who take many other medications. In these specific clinical circumstances, GBP's pharmacokinetic profile (not metabolized, no significant drug-drug interactions or protein binding, and lack of organ toxicity) has been advocated as a main advantage over the other adjuvant analgesics.

However, the elderly may be more susceptible to GBP-induced side effects [20, 31, 34-36, 46]. Decreased mental alertness or awareness is possible at higher doses. Low starting dose, dosage adjustment and slow titration are recommended to decrease the frequency of side effects in this population. Also, multiple daily dosing of GBP has the potential to reduce compliance in these populations.

When considering cost, traditional agents (tricyclic antidepressants and older anticonvulsants), which may be available in generic formulations, are less expensive [20, 22, 43, 46]. However, it is possible that the higher cost associated with GBP may be offset by better tolerability and improved quality of life obtained with this agent as compared with the other adjunct analgesics. Significant cost may be incurred by patients taking the highest dosages of GBP [65].

The RCT data for patients with PHN or PDN has been used as a strong argument for recommending GBP as a first line treatment option in the management of other forms of neuropathic pain [31, 61]. However, its efficacy for states other than PHN and PDN has yet to be established. To date, the supporting evidence has been obtained only from several small sample placebo-controlled RCTs on the use of GBP for various NMCP states, with potential for bias because of methodological limitations [22, 31, 58].

None of the published RCTs compared the therapeutic effects of GBP on individual pain symptoms [22, 31, 58]. Uncontrolled and open-label studies suggest that GBP is particularly helpful in reducing paroxysmal pain with lancinating and burning

quality [58]. However, the evidence clearly linking efficacy of GBP to individual pain symptoms is yet to be obtained [18, 31, 56-58]. It is not clear yet whether GBP would be more effective in controlling burning pain and paroxysmal pain than antidepressants [18, 20, 27, 31, 32, 57, 58, 63].

CONCLUSION

Based on the available evidence, GBP (Neurontin®) has been shown to be effective, safe and well tolerated in patients with PHN and PDN. To date, it has been reported to be superior to placebo in PHN and PDN (in doses up to 3,600 mg/day, for 8 weeks) and equivalent to amitriptyline in PDN (in doses up to 1,800 mg/day, for 6 weeks).

However, at present more data are needed to support the use of GBP as first-line medication for the management of neuropathic pain with a better efficacy, fewer side effects and a favorable cost-efficiency ratio as compared to alternative medications. Although the overall efficacy, safety and tolerability data are generally favorable when compared to placebo, GBP does not appear to offer any considerable advantages over antidepressants and older anticonvulsants, which are cheaper medications.

Because of its pharmacokinetic profile and safety record, GBP may represent an alternative for patients in whom traditional agents were contraindicated, intolerable or ineffective. However, those considering it as an alternative should be aware that the durability of pain relief and long-term safety and tolerability of GBP are still unknown.

Well-designed, large and long-term RCTs are needed to determine the place of GBP in relation to alternative options for various types of neuropathic pain. The cost-effectiveness of GBP and the use of this agent as an adjunct therapy have yet to be studied, and trials which include therapeutic drug monitoring are needed to individualize the dosing.

In Canada regulatory indications for GBP (Neurontin®) are currently limited to the treatment of epilepsy and in the USA it is also approved for PHN. Increasing evidence indicates that GBP is promising in the treatment of several other NMCP states. Data from ongoing and future research may better establish the role of GBP in the management of NMCP.

Health Technology Assessment Unit
Alberta Heritage Foundation for Medical Research
Contact: Paula Corabian, Tel: (780) 423-5727, Fax: (780) 429-3509

Technotes are brief reports, prepared on an urgent basis, which draw on limited reviews and analysis of relevant literature and on expert opinion and regulatory status where appropriate. They are not subject to an external review process.

APPENDIX A: METHODOLOGY

Search Strategy

A computer search of relevant databases for published articles on the safety and analgesic efficacy/effectiveness of using gabapentin (GBP) in the management of patients (any age) with non-malignant chronic pain (NMCP) was conducted. The following major electronic databases were searched between April 5 and April 16, 2004: Cochrane Library (Issue 1, 2004), NHS Centre for Reviews and Dissemination databases (HTA, NHSEED, and DARE), PubMed, and EMBASE. In addition, relevant library collections, web sites of clinical trials, clinical practice guidelines, regulatory agencies, evidence-based resources and other HTA related agency resources (AETMIS, CCOHTA, ECRI) were searched. Internet search engines were also used to locate grey literature.

The keywords (used alone or in combination) for the above mentioned searches included: gabapentin, neurontin, pain, migraine, headache, fibromyalgia, back pain, neuropathy, and neuralgia.

Searches were limited to human, English language, and publication dates 1999 to 2004.

In addition to the above mentioned searches, the bibliographies and reference lists from the selected and retrieved articles were examined.

Canadian specialists in pain management were contacted for clinical input on the current status of using GBP for NMCP. At the time of the completion of this report, no advice from the Canadian specialists was received.

Health Canada was contacted for information on regulatory status of GBP in Canada.

Screening and Reviewing the Literature

The studies identified by the search strategy were retrieved, reviewed and assessed to determine the relevance of each study by one reviewer. Their inclusion/exclusion was decided by one reviewer. Suitability for inclusion in the report was determined on the basis of a list of criteria developed for this study.

Considered for inclusion were published reports of systematic reviews (quantitative and/or qualitative) of primary research that evaluated the safety and efficacy/effectiveness of using GBP in comparison to placebo or any other pharmacological or non-pharmacological treatment used in the management of NMCP.

Using criteria from Cook et al. [54], **a review was considered to be systematic if** it met the following criteria:

- focused clinical question;
- explicit search strategy;

- use of explicit, reproducible and uniformly applied criteria for article selection;
- critical appraisal of the included studies;
- qualitative or quantitative data synthesis.

Published reports of systematic reviews **were excluded** *if*:

- they focused on the use of GBP to treat acute pain, post-operative pain or cancer-related pain;
- they reviewed studies including patients with various types of pain, and the data on the use of GBP for NMCP were not reported separately;
- they focused on the use of GBP for other non-epileptic conditions (such as bipolar disorder);
- they reviewed studies on the use of GBP for NMCP and for other non-epileptic condition and the data were not reported separately.

Published reports of reviews, which summarized the research on the use of GBP for NMCP but lacked an explicit description of a systematic approach to the identification and interpretation of evidence, were excluded from data extraction (Table 1). They were considered only as a source for background information (including narrative and descriptive reviews).

Clinical reviews, commentaries and discussion papers on NMCP and/or on the use of GBP for NMCP were also included as a source for background information.

Published reports of primary research studies (including RCTs), editorials, letters and technical reports **were also excluded**.

Table 1: Summary of the final exclusion process based on the full text article

Study	Reason for Exclusion
Dworkin et al. 2003 [31]	It did not meet all the criteria for a systematic review.
Mack (2003) [22]	It did not meet all the criteria for a systematic review.
Stacey & Glanzman (2003) [40]	It did not meet all the criteria for a systematic review.
Scheinfeld (2003) [26]	It did not meet all the criteria for a systematic review.
Backonja (2003) [28]	It did not meet all the criteria for a systematic review.
Pappagallo (2003) [47]	It did not meet all the criteria for a systematic review.
Backonja & Glanzman [21]	It did not meet all the criteria for a systematic review.
Krymchantowski et al. (2002) [24]	It did not meet all the criteria for a systematic review.

Table 1: Summary of the final exclusion process based on the full text article (cont'd)

Study	Reason for Exclusion
Alper & Lewis (2002) [48]	It reviewed one RCT on GBP, also included in all systematic reviews considered for this study [56, 57, 58]
Hemstreet & Lapointe (2001) [45]	It did not meet all the criteria for a systematic review.
Laird & Gidal (2000) [46]	It did not meet all the criteria for a systematic review.
Sindrup & Jensen (2000) [50]	It did not meet all the criteria for a systematic review.
Tremont et al. (2000) [44]	It did not meet all the criteria for a systematic review.
Rawn et al. (2000) [43]	It did not meet all the criteria for a systematic review.

Main characteristics, findings and conclusions from published reports of the selected systematic reviews and details of their methodology were summarized in tabular form (see Appendix B, Tables 2 and 3). The methodological quality of these studies was not critically appraised and no attempt was made to assess the validity of their findings.

APPENDIX B: RESULTS REPORTED BY SYSTEMATIC REVIEWS

Abbreviations

CI – 95% confidence interval

GBP –gabapentin

mg – milligrams

mo – month(s)

n – number of participants/patients in the reviewed trials

NNT – numbers-needed-to-treat

NNH – numbers-needed-to-harm

NS - not statistically significant;

RB – relative benefit

RCT – randomized controlled trial

RR – relative risk

SD - standard deviation

SF-36 – Short Form 36 Health Survey

SF-MPQ – Short Form McGill pain Questionnaire

SS – statistically significant

SSRIs – selective serotonin reuptake inhibitors

TA – tricyclic antidepressants

TN – trigeminal neuralgia

UK - United Kingdom

VAS - visual analogue scale

vs – versus

WMD – weighted mean difference

wk -week(s)

y – year(s)

Table 2: Systematic reviews (characteristics and main findings and conclusions)

Study	Study's characteristics	Study's main findings* and conclusions**
Wiffen et al., 2000 [56] Cochrane Systematic Review	**Included studies:** RCTs of anticonvulsant drugs in acute, chronic, and cancer pain, with pain assessment as either the primary or secondary outcome **Excluded studies:** non-RCTs, studies of experimental pain, case reports, clinical observations, studies of anticonvulsants used to treat pain produced by other drugs, studies of anticonvulsants used for migraine or headache. **Participants:** adults (18 y to 84 y); chronic pain included TN, PHN, diabetic neuropathy, central pain after stroke, irritable bowel and temporomandibular joint dysfunction. **Intervention:** administration of anticonvulsant drugs. **Comparator(s):** the reviewed studies used placebo, other drugs. **Outcome(s) and outcome measures:** analgesic effect; NNT calculated for effectiveness, adverse effects and drug-related study withdrawal;	**Main Findings*** **Only 2/23 selected RCTs studied GBP for NMCP. **One **placebo**-controlled RCT of **GBP** in **PHN** (n=229, age ≥ 18y, PHN for >3 mo) had an NNT for effectiveness of 3.2 (CI 2.4-5.0); 43% of patients improved on GBP (a global improvement scale). **One **placebo**-controlled RCT of **GBP** for **PDN** (n=165 patients, mean age 53y) had an NNT for effectiveness of 3.8 (CI 2.4- 8.7); 60% of patients improved on GBP (global improvement scale). **NNH for "minor harm" was NSS for GBP or any of the drugs evaluated. **NNH for "minor harm" was 2.5 (CI 2.0-3.2) for GBP. **Conclusions**** "Although anticonvulsants are used widely in chronic pain surprisingly few trials show analgesic effectiveness. No trial compared different anticonvulsants." "In chronic pain syndromes other than trigeminal neuralgia, anticonvulsants should be withheld until other interventions have been tried. While gabapentin is increasingly being used for neuropathic pain the evidence would suggest that it is not superior to carbamazepine."

* Only main findings regarding the intervention of interest (administration of GBP) are summarized;
** Conclusion(s) summarized the conclusions stated by the author(s) or quoted them exactly as in the published report

Table 2: Systematic reviews (characteristics and main findings and conclusions) (cont'd)

Study	Study's characteristics	Study's main findings* and conclusions**
Collins et al., 2000 [57] United Kingdom	**Included studies:** published double-blind RCTs of antidepressants and anticonvulsants for PHN and PDN **Excluded studies:** not clearly stated **Participants:** adults with PDN or PHN (conditions defined by authors of original trials; adequate description diagnostic criteria) **Intervention:** administration of antidepressants or anticonvulsants **Comparator(s):** placebo **Outcome(s) and outcome measure(s):** analgesic effect; improvement on a measure of effectiveness equivalent to at least 50% pain relief; RB, RR and NNT calculated for effectiveness, adverse effects and drug-related study withdrawal;	**Main Findings*** ***GBP vs other anticonvulsants (phenytoin and carbamazepine)*** **In **PDN**: 4 **placebo**-controlled RCTs on anticonvulsants (321 patient episodes); one of these four RCTs evaluated the use of GBP (n=165 patients); **In **PHN**: 1 **placebo**-controlled RCT on GBP (225 patient episodes); **All anticonvulsants were superior to placebo: RB for GBP of 2.4 (CI 1.8-3.3) and RB for phenytoin/carbamazepine of 3.4 (CI 2.1-5.4); NNT for GBP of 3.4 (CI 2.1-5.4) and for phenytoin/carbamazepine of 2.2 (CI 1.7-3.1); **GBP and phenytoin showed a SS increase in incidence of minor adverse effects when compared to placebo: RR of 2.4 (CI 1.9-3.0) and 4.2 (CI 2.0-8.9), respectively; NNH of 2.6 (CI 2.1-3.3) and 3.2 (CI 2.1-6.3), respectively; the benefit/minor harm ratio for both GBP and phenytoin was 1 **Neither GBP nor phenytoin/carbamazepine showed a SS difference over placebo in major adverse effects; the benefit/major harm ratio of 6 for GBP and of 9 for phenytoin/carbamazepine **Conclusions**** "Antidepressants and anticonvulsants had the same efficacy and incidence of minor adverse effects in these two neuropathic pain conditions". There was no evidence "that gabapentin was better than older anticonvulsants". In the reviewed RCTs, "patients were more likely to stop taking antidepressants than anticonvulsants because of adverse effects."

* Only main findings regarding the intervention of interest (administration of GBP) are summarized;
** Conclusion(s) summarized the conclusions stated by the author(s) or quoted them exactly as in the published report

Table 2: Systematic reviews (characteristics and main findings and conclusions) (cont'd)

Study	Study's characteristics	Study's main findings* and conclusions**
Mellegers et al., 2001 [58] Canada and The Netherlands	**Included studies:** uncontrolled and controlled clinical trials (RCTs) of GBP for neuropathic pain. **Excluded studies:** abstracts and preliminary results. **Participants:** patients with any kind of neuropathic pain. **Intervention:** GBP administered alone or in conjunction with other drugs **Comparator(s):** not clearly stated but the reviewed studies used placebo, other drugs. **Outcome(s) and outcome measure(s):** analgesic effect; statistical pooling of data reported on pain relief; QOL; subjects' global impression of change; clinicians' global impression of change; side effects.	**Main Findings*** ***Uncontrolled studies*** **30 studies included; 26 populations with neuropathic pain syndromes such as **CP, CRPS, TN, mixed nociceptive and neuropathic pain, mixed types of neuropathic pain** (n=395 patients); **Overall, 314/395 patients (79.5%) experienced "meaningful" pain relief with GBP. **Side effects in 29.3% of GBP-treated patients; intolerable side effects resulting in withdrawal from study were reported in 4.4% of GBP-treated patients; ***Controlled trials*** **Six RCTs included: 1 RCT compared **GBP vs. placebo** in **PHN**, 3 RCTs compared **GBP vs. placebo** in **PDN**, and 2 RCTs compared **GBP vs. amitriptyline** in **PDN**; **Statistically pooled data from 4 **placebo**-controlled RCTs (n=235 patients with **PDN** and n=229 patients with **PHN**) showed an RB of 2.5 (CI fixed: 1.9, 3.4) for GBP (in terms of "number of patients reporting moderate or excellent pain relief); **Statistically pooled data from 2 **placebo**-controlled RCTs (n=229 patients with **PHN** and n=165 patients with **PDN**) showed a weighted VAS mean difference of –11.1 mm for GBP (CI fixed: -13.2, -11.1); a weighted final SF-MPQ mean difference of –5.89 for GBP (CI: -6.20, -5.59); an RB in subjects' global impression of change of 2.44 for GBP (CI:1.8, 3.31); and an RB in clinicians' global impression of change of 2.65 for GBP(CI: 1.86, 3.78); **The RCT in **PHN** reported side effects in 54.9% of GBP-treated patients and in 27.6% of **placebo**-treated patients; intolerable side effects resulting in withdrawal from study were reported in 10.5% of GBP treated patients and in 6.1% of those receiving placebo; **Conclusions**** "Gabapentin seems to be effective in multiple painful neuropathic conditions. The variable prescribing patterns of the uncontrolled studies raise the suspicion that effectiveness may be reduced if one limits administration of the drug to very low dosages, whereas rapid dose escalation may be associated with increased central nervous system side effects. Well-designed controlled trials may provide insight into different symptom sensitivity to the drug."

* Only main findings regarding the intervention of interest (administration of GBP) are summarized;
** Conclusion(s) summarized the conclusions stated by the author(s) or quoted them exactly as in the published report

Table 3: Objective(s) and methods of selected systematic reviews

Study	Study's objective(s) and methods
Wiffen et al. 2000 [56] Cochrane Systematic Review	**Objective:** To evaluate the analgesic effectiveness and adverse effects of anticonvulsant drugs for pain management in clinical practice and to identify a clinical research agenda. **Methods:** **Date of most recent search: September 1999 (using Cochrane Pain, Palliative Care and Supportive Care Group search strategy). **RCTs of anticonvulsants in acute, chronic or cancer pain were identified by Medline (1966-1999), Embase (1994-1999), SIGLE (1980-1999) and the Cochrane Controlled Trials Register (CENTRAL/CCTR) (Cochrane Library Issue 3, 1999); 40 medical journals were hand searched; additional reports identified from reference list of retrieved papers, and by contacting investigators. Search was narrowed to include specific anticonvulsant drugs. **Eligibility was determined by reading each report identified by the search. All the authors read all reports and agreement were reached by discussion. **Two independent reviewers extracted data. **RCTs were quality scored independently by 4 of the authors using a 3-item scale (Jadad et al, 1996), who then met to agree a "consensus" score for each study. The scores were not used to weigh the results. **NNT were calculated as the reciprocal of the absolute risk reduction; for unwanted effects, the NNT becomes NNH (and is calculated in the same way); NNT were calculated from dichotomous data for effectiveness, adverse effects and drug-related study withdrawal, for individual studies and for pooled data; **NNH were calculated, where possible, by combining studies for each drug entity irrespective of the condition treated; NNH were calculated for "major harm" (any effect leading to withdrawal from the study) and for "minor harm" (including symptoms such as drowsiness, dizziness, constipation, nausea, and ataxia)

Table 3: Objective(s) and methods of selected systematic reviews (cont'd)

Study	Study's objective(s) and methods
Collins et al., 2000 [57] United Kingdom	**Objective:** To determine the relative efficacy and adverse effects of antidepressants and anticonvulsants in the treatment of diabetic neuroapathy and postherpetic neuralgia; **Methods:** searches of 2 systematic reviews published previously were updated searching for published RCTs of antidepressants and anticonvulsants in diabetic neuropathy and PHN. **Medline('93-'99), EMBASE('94-'99), CINAHL('82-99), the Cochrane Library (issue 1, '99) and the Oxford Pain Relief Database ('50-'99) were searched using the following keywords: 'anti*depressant*", "tricycli*", "SSRI*", "selective serotonin re*uptake inhibitor*" , "MAOI*", "mono*",amine*oxidase inhibitor", "anticonvulsant*", 'anti*epileptic*", "random", "trials, "study", "studies", "analgesi*", "pain*", "neuropath*", "neuralgia", 55 generic names of antidepressants and 33 generic names of anticonvulsants (braod text search without restriction to language); additional reports were identified from reference lists of retrieved articles and reviews; unpublished data was not sought; **For each study data was extracted for condition studied, number of enrolled and analyzed patients, study design, study duration, dosing regimen, outcome measures used for pain, reported analgesic outcomes, minor adverse effects (not resulting in withdrawal from study), major adverse effects (resulting in withdrawal from study) and other withdrawals not related to adverse effects; **Each report was read and scored using a 3-item 105 score quality scale (Jadad et al, 1996). **Clinically relevant outcome defined as improvement on a measure of effectiveness equivalent to at least 50% pain relief; **The RB and NNT for one patient to achieve at least 50 % pain relief (when compared to placebo) was calculated from available dichotomous data, as was the RR and NNH for minor adverse effects and major adverse effects (drug related study withdrawal); RB and RR estimates with 95% CI were calculated using a fixed effects model; a SS difference between active treatment and placebo was assumed when the lower limit of 95% CI of the RR was >1; NNT and NNH with 95% CI were calculated by the method of Cook and Sackett; **Treatment benefit/harm ratios were calculated where possible by dividing the absolute risk reduction for benefit (efficacy) by the absolute risk reduction for harm (minor and major adverse effects); **Calculations performed using Excel 98 on an iMac.

Table 3: Objective(s) and methods of selected systematic reviews (cont'd)

Study	Study's objective(s) and methods
Mellegers et al., 2001 [58] Canada and The Netherlands	**Objective:** To assess the efficacy/effectiveness and side effects of gabapentin for the treatment of neuropathic pain; **Methods:** **Search of electronic databases (Cochrane Controlled Trial Register, issue 1, 2001; Excerpta Medica using EMBASE from 1980 to March 2001; Index Medicus via MEDLINE from 1966 to March 2001; Science Citation Index from 1993 to September 1999); no language restriction applied; keywords included pain, nociceptors, analgesic, neuropathy, neuropathic, allodynia, hyperalgesia, gabapentin, and Neurontin; reference lists in retrieved papers/documents/book chapters were also searched; personal communication with content experts was used. **Included were published reports of RCTs and non-RCTs, case series and case reports, on the use of GBP for relief of any kind of neuropathic pain; abstracts and preliminary results were excluded. **Data extracted by one reviewer and double-checked by a second reviewer. Authors were contacted by letter when insufficient data were reported in the published studies. **Quality of controlled studies was assessed independently by 2 reviewers using 3-item score system developed by Jadad et al. (1996), who met in case of disagreement for consensus. **For controlled trials, efficacy of GBP was assessed through a meta-analysis of RCT data (continuous and dichotomous outcomes extracted and entered in RevMan 4.1); clinically and statistically homogenous data were pooled and analyzed using fixed effects model and presented as relative benefit (with CI) for dichotomous outcomes, and WMD (with CI) for continuous outcomes; sensitivity analysis conducted. **The quality of the uncontrolled studies was assessed by all three reviewers using a questionnaire they developed, which contained items judged to be appropriate for their study. **The effectiveness of GBP in uncontrolled studies was assessed via a system of dichotomous classification of "bad" ("nonmeaningful" pain relief) vs."good" ("meaningful" pain relief) results; due to heterogeneity of outcomes, "meaningful relief" included (1) SS changes in multiple quantitatively measured outcomes, (2) "good" to "excellent" pain relief in well defined categorical outcomes and (3) "worthwhile" relief obtained through narratives, as per consensus judgment of all 3 reviewers.

REFERENCES

1. Perkin GD. Trigeminal Neuralgia. *Curr Treat Options Neurol* 1999;1(5):458-65.
2. Ospina M, Harstall C. *Prevalence of chronic pain: an overview.* Health Technology Assessment Unit, editor. Edmonton, AB: Alberta Heritage Foundation for Medical Research; 2002: HTA29.
3. Ospina M, Harstall C. *Multidisciplinary pain programs for chronic pain: evidence from systematic reviews.* Health Technology Assessment Unit, editor. Edmonton, AB: Alberta Heritage Foundation for Medical Research; 2003: HTA 30.
4. Marcus DA. *Treatment of nonmalignant chronic pain.* National Headache Foundation and Bloch Education Foundation, editor. Pittsburgh, PA: 2001.
5. MacKinnon GE, Swanson L. *Pharmacologic treatment of chronic pain.* Midwestern University College of Pharmacy - Glendale, editor. Phoenix, AZ: InetCE; 2003;7(4).
6. Merck. Pain: a complex subjective sensation reflecting real or potential tissue damage and the effective response to it. Available: *http://www.merck.com/mrkshared/mmanual/section14/chapter.167/167a.jsp* (accessed 2004 May 7).
7. Merck. Neuropathic pain. Available: *http://www.merck.com/mrkshared/mmanual/section14/chapter.167/167d.jsp* (accessed 2004 May 7).
8. Feinberg SD. *ACPA Medications & Chronic Pain. Supplement 2004.* American Chronic Pain Association, editor. Rocklin, CA: American Chronic Pain Association; 2003.
9. Scott A. *Trigger point injections for non-malignant chronic pain.* Health Technology Assessment Unit, editor. Edmonton, AB: Alberta Heritage Foundation for Medical Research; 2002: TN 39.
10. Chronic Pain Association of Canada. Pain: full facts. Available: *http://ecn.ab.ca/cpac/page5.html* (accessed 2003 Mar 14).
11. Alberta Health and Wellness. *Chronic pain in Alberta: a portrait from the 1996 National Population Health Survey and the 2001 Canadian Community Health Survey.* Health Surveillance, editor. Edmonton, AB: Alberta Health and Wellness; 2003.
12. Harstall C. *Use of cannabis or cannabinoids for non-malignant chronic pain.* Health Technology Assessment Unit, editor. Edmonton, AB: Alberta Heritage Foundation for Medical Research; 2004: TN 42.
13. Merck. Psychogenic pain syndromes. Available: *http://www.merck.com/mrkshared/mmanual/section14/chapter.167/167e.jsp* (accessed 2004 May 7).

14. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. *Anaesthesia* 2002;57(5):451-62.

15. Mathew NT, Hulihan JF, Rothrock JF. Anticonvulsants in migraine prophylaxis. *Neurology* 2003;. 60(7 Suppl 2):S45-S49.

16. Nicholson B. Gabapentin use in neuropathic pain syndromes. *Acta Neurol Scand* 2000;101(6):359-71.

17. Finnerup NB, Gottrup H, Jensen TS. Anticonvulsants in central pain. *Expert Opin Pharmacother* 2002;3(10):1411-20.

18. Mao J, Chen LL. Gabapentin in pain management. *Anesth Analg* 2000;91(3):680-7.

19. Diener HC, Limmroth V. Advances in pharmacological treatment of migraine. *Expert Opin Investig Drugs* 2001;10(10):1831-45.

20. Rosenquist RW. Gabapentin. *J Am Acad Orthop Surg* 2002;10(3):153-6.

21. Backonja M, Glanzman RL. Gabapentin dosing for neuropathic pain: evidence from randomized, placebo-controlled clinical trials. *Clin Ther* 2003;25(1):81-104.

22. Mack A. Examination of the evidence for off-label use of gabapentin. *J Manag Care Pharm* 2003;9(6):559-68.

23. Surges R, Feuerstein TJ. Mode of action of gabapentin in chronic neuropathic pain syndromes. A short review about its cellular mechanisms in nociceptive neurotransmission. *Arzneimittelforschung* 2002;52(8):583-6.

24. Krymchantowski AV, Bigal ME, Moreira PF. New and emerging prophylactic agents for migraine. *CNS Drugs* 2002;16(9):611-34.

25. Gilron I. Gabapentin: a viewpoint by Ian Gilron. *CNS Drugs* 2003;17(13):983-4.

26. Scheinfeld N. The role of gabapentin in treating diseases with cutaneous manifestations and pain. *Int J Dermatol* 2003;42(6):491-5.

27. Backonja MM. Use of anticonvulsants for treatment of neuropathic pain. *Neurology* 2002;59(5 Suppl 2):S14-S17.

28. Backonja M. Anticonvulsants for the treatment of neuropathic pain syndromes. *Curr Pain Headache Rep* 2003;7(1):39-42.

29. Jensen TS. Anticonvulsants in neuropathic pain: rationale and clinical evidence. *Eur J Pain* 2002;6(Suppl A):61-8.

30. Hempenstall K, Rice ASC. Current treatment options in neuropathic pain. *Curr Opin in Invest Drugs* 2002;. 3(3):441-8.

31. Dworkin RH, Backonja M, Rowbotham MC, Allen RR, Argoff CR, Bennett GJ, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Arch Neurol* 2003;60(11):1524-34.

32. Wheeler G. Gabapentin. Pfizer. *Curr Opin Investig Drugs* 2002;3(3):470-7.

33. Neurontin® . *Compendium of Pharmaceuticals and Specialties (CPS)* 2004.

34. Mosby's Drug Consult. Gabapentin. Available: *http://home.mdconsult.com/das/drug/body/260607172/1/3175.html* (accessed 2004 Apr 7).

35. Medline Plus. Drug information: gabapentin (systemic). Available: *http://www.nlm.nih.gov/medlineplus/print/druginfo/uspdi/202732.html* (accessed 2004 Jul 6).

36. Matrix Direct Insurance Services. Gabapentin. Available: *http://www.rxlist.com/cgi/generic/gabapent_ids.htm* (accessed 2004 Jul 6).

37. Health Canada. Drug Product Database (DPD). Available: *http://search.hc-sc.gc.ca* (accessed 2004 Apr 5).

38. Tennyson H, Levine N. Neurotropic and psychotropic drugs in dermatology. *Dermatol Clin* 2001;19(1):179-97.

39. Curran MP, Wagstaff AJ. Gabapentin: in postherpetic neuralgia. *CNS Drugs* 2003;17(13):975-82.

40. Stacey BR. Gabapentin: a viewpoint by Brett R. Stacey. *CNS Drugs* 2003;17(13):983.

41. Johnson RW. Herpes zoster in the immunocompetent patient: management of post-herpetic neuralgia. *Herpes* 2003;10(2):38-45.

42. Corbo J. The role of anticonvulsants in preventive migraine therapy. *Curr Pain Headache Rep* 2003;7(1):63-6.

43. Rawn T, Papoushek C, Evans MF. Gabapentin or amitriptyline for painful diabetic neuropathy? *Can Fam Physician* 2000;46:2215-7

44. Tremont-Lukats IW, Megeff C, Backonja MM. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. *Drugs* 2000;60(5):1029-52.

45. Hemstreet B, Lapointe M. Evidence for the use of gabapentin in the treatment of diabetic peripheral neuropathy. *Clin Ther* 2001;23(4):520-31.

46. Laird MA, Gidal BE. Use of gabapentin in the treatment of neuropathic pain. *Ann Pharmacother* 2000;34(6):802-7.

47. Pappagallo M. Newer antiepileptic drugs: possible uses in the treatment of neuropathic pain and migraine. *Clin Ther* 2003;25(10):2506-38.

48. Alper BS, Lewis PR. Treatment of postherpetic neuralgia: a systematic review of the literature. *J Fam Pract* 2002;51(2):121-8.

49. Pappagallo M, Haldey EJ. Pharmacological management of postherpetic neuralgia. *CNS Drugs* 2003;17(11):771-80.

50. Sindrup SH, Jensen TS. Pharmacologic treatment of pain in polyneuropathy. *Neurology* 2000;55(7):915-20.

51. Frediani F, Cominelli F, Sgarzi M. Anticonvulsant drugs in migraine prophylaxis. *J Headache & Pain* 2001; 2(Suppl 1):S121-S124.

52. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Drug approvals for May 2002. Available: *http://www.fda.gov/cder/da/da0502.htm* (accessed 2004 Jun 16).

53. Oxman A, Guyatt GH, Cook D, Montori V. Summarizing the evidence. In: Guyatt GH, Rennie D, editors. *Users' Guides to the Medical Literature: a manual for evidence-based clinical practice.* Chicago, IL: AMA Press; 2002:155-73.

54. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med* 1997;126:155-73.

55. Centre for Evidence-Based Medicine. Levels of evidence and grades of recommendations. Available: *http:/www.cebm.net* (accessed 2004 Mar 5).

56. Wiffen P, Collins S, McQuay H, Carroll D, Jadad A, Moore A. Anticonvulsant drugs for acute and chronic pain. In: *The Cochrane Library,* Issue 1, 2004.

57. Collins SL, Moore RA, McQuayHJ, Wiffen P. Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review. *J Pain Symptom Manage* 2000;20(6):449-58.

58. Mellegers MA, Furlan AD, Mailis A. Gabapentin for neuropathic pain: systematic review of controlled and uncontrolled literature. *Clin J Pain* 2001;17(4):284-95.

59. Chronicle E, Mulleners W. Anticonvulsant drugs for migraine prophylaxis (Protocol for a Cochrane Review). In: *The Cochrane Library* Issue 2, 2004.

60. Rog DJ, Young C. Treatment of neuropathic pain for Multiple Sclerosis (Protocol for a Cochrane Review). In: *The Cochrane Library* Issue 2, 2004.

61. Washington Department of Labor and Industries. Guideline for the use of Neurontin in the management of neuropathic pain. Available: *http://ngc.gov/summary/summary.aspx?ss=15&doc_id=3550&nbr=2776&string=gabapentin* (accessed 4-7-2004). Seattle, WA; Washington Department of Labor and Industries, Washington State Medical Association.

62. Danshaw CB. An anesthetic approach to amputation and pain syndromes. *Phys Med Rehabil Clin N Am* 2000;11(3):553-7.

63. Vickers ER, Cousins MJ. Neuropathic orofacial pain. Part 2-Diagnostic procedures, treatment guidelines and case reports. *Aust Endod J* 2000;26(2):53-63.

64. Chan PSL, Clark AJ. Postherpetic neuralgia: Review of treatment modalities. *Pain Res & Manage* 2000;5(1):69-74.

65. Adelman JU, Adelman LC, Von Seggern R. Cost-effectiveness of antiepileptic drugs in migraine prophylaxis. *Headache* 2002;. 42(10):978-83.